



Alessie, R., Angelini, V., van den Berg, G. J., Mierau, J., & Viluma, L. (2019). Economic conditions at birth and cardiovascular disease risk in adulthood: Evidence from post-1950 cohorts. *Social Science and Medicine*, 224, 77-84.
<https://doi.org/10.1016/j.socscimed.2019.02.006>

Peer reviewed version

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Link to published version (if available):
[10.1016/j.socscimed.2019.02.006](https://doi.org/10.1016/j.socscimed.2019.02.006)

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ECONOMIC CONDITIONS AT BIRTH AND CARDIOVASCULAR DISEASE RISK IN ADULTHOOD: EVIDENCE FROM POST-1950 COHORTS

SEPTEMBER 2018

ABSTRACT

Much of the literature that studies long-run effects of early-life economic conditions on health outcomes is based on pre-1940 birth cohorts. Early in these individuals' lives, public social safety nets were at best rudimentary, and female labor force participation was relatively low. We complement the evidence by studying the effects of regional business cycle variations in the post-1950 Netherlands on cardiovascular disease risk in adulthood.

We use data from Lifelines, a large cohort study that covers socio-economic, biological and health information from over 75,000 individuals aged between 20 and 63. Cardiovascular risk index is constructed from an extensive set of biomarkers.

The results show that for women a 1 p.p. increase in the provincial unemployment level leads to a 0.02 p.p. increase in the risk of a fatal cardiovascular event in the coming 10 years while the effect in men is not significant. We conclude that women born in adverse economic conditions experience higher cardiovascular risk.

KEYWORDS: early-life conditions, developmental origins, recession, health, unemployment, long-run effects, biomarkers.

JEL-CODES: I10; I15; J11

1. Introduction

An expanding body of literature has documented negative effects of adverse economic conditions around the time of birth on a range of late-life mortality and morbidity outcomes (see, for instance, Doblhammer *et al.*, 2013; van den Berg *et al.*, 2006, 2009, 2011, 2013; Lindeboom *et al.*, 2010). Our paper adds to this literature by studying the effect of economic conditions at the time of birth on cardiovascular health in adulthood in post-1950 cohorts. This literature stems from the fetal programming hypothesis – alternatively referred to as the critical period, biological imprint, biological embedding or developmental origins hypothesis – which suggests that certain exposures early in life permanently and irreversibly alter the structure and/or function of organs, tissues and systems (Barker, 1995; Rasmussen *et al.*, 2001; Kuh and Hardy, 2002; Kuh and Ben-Shlomo, 2004; Case *et al.*, 2005; Wadhwa *et al.*, 2009). Barker (1995) argued that nutritional shocks in utero force the fetus to adapt in order to sustain its development and these adaptations may be permanent, for example, redirecting oxygenated blood away from the body to sustain brain, which leads to underdeveloped liver function and raised cholesterol levels in adult life. Such mechanisms can be seen as a predictive adaptive response to the future environment (van den Berg *et al.*, 2015). Advances in the field of epigenetics are revealing that this adaptation might happen through gene expression in humans that persists throughout life. So for example, children conceived during the Dutch Hunger Winter are considered to have survived the adverse prenatal circumstances thanks to adjustments in their DNA (Heijmans *et al.*, 2008). Their genes had adjusted to promote growth; however, as a result later in life these children have an increased risk of high cholesterol, diabetes and even schizophrenia.

Economic models (Becker 1960, 1965; Dehejia and Lleras-Muney, 2004) predict that the economic conditions can affect the health of fetuses and infants in several ways. First, economic hardship such as increase in unemployment might affect the household income and cause reductions in consumption, leading to lower quantity and quality of food and prenatal care

consumed by pregnant women. However, high unemployment may also cause changes in other health-related consumption, such as smoking and alcohol, and changes in time use, where pregnant women might have more time for time intensive healthy activities, such as exercise or cooking (Deheija and Lleras-Muney, 2004, Ruhm, 2000, 2005). Besides, economic hardship might induce financial stress in some (Alessie et al., 2018), while also reducing work-related stress in others (van den Berg et al., 2018). In addition, changes in cohort composition may play a role. If low socioeconomic status (SES) families postpone fertility during periods economic hardship more than high SES families, the average health of the individuals that are born might even improve (Deheija and Lleras-Muney, 2004, Alessie *et al.*, 2018, van den Berg *et al.*, 2018).

This paper studies the effect of economic conditions at the time of birth on cardiovascular health in adulthood in post-1950 cohorts. To avoid endogeneity problems with the use of measures of economic conditions in the individual household, many studies, including ours, exploit exogenous variation in contextual conditions, such as the state of the business cycle at birth, as an indicator of the economic conditions that the households face (see, for instance, van den Berg *et al.*, 2006, 2009, 2011, 2013, Angelini and Mierau, 2014, Cutler *et al.*, 2016, and the overviews in Almond and Currie, 2011 and van den Berg and Lindeboom, 2014). This literature focuses predominantly on over-all or cause-specific mortality as outcome measures, because mortality data is objective, reliable and readily available. However, since mortality is an end-state phenomenon, these analyses necessarily examine cohorts born before World War II. There are several reasons why the findings from this time frame might not be applicable to the current cohorts.

First, it is possible that the extent to which an economic downturn leads to adverse economic conditions within households may be smaller for cohorts born after World War II. Western European countries have established social safety nets that include relatively generous

unemployment benefits and welfare payments for those without work. This could mean that the business cycle has become a weaker indicator for economic shocks in the household.

Second, the nature of the effects of economic conditions might have changed. Since the social safety nets protect households from sudden income losses and, hence, deprivation and malnutrition, other mechanisms become important instead. For instance, an economic downturn may increase stress, fear of job loss, or lower opportunity costs of pregnancy. The consequences of these exposures might be different from the effects of business cycle fluctuations without the social safety nets.

Third, compared to pre-war birth cohorts, in modern cohorts female labor force participation in adulthood tends to be higher. This may alter the effect of business cycle fluctuations in more recent birth cohorts, through increased prenatal stress exposure of the mothers. In addition, the long-run effects on cohorts of daughters may depend on their own exposure to labor market fluctuations later in their life. All this may lead to changes in the size of average long-run effects of business cycles across eras, and these changes might differ between men and women. Nevertheless, the size and direction of the changes remains an empirical question that we address in this paper.

Another reason to expect different effects among men and women is the well-documented gender differences in effects of the conditions early in life. Biological evidence documents gender-differences in fetal sensitivity (Catalano *et al.*, 2005) which may be driven by different intra-uterine growth strategies between male and female fetuses (see, Eriksson *et al.*, 2010). Focusing on the effects of the business cycle, studies with cohorts born a long time ago tend to find smaller over-all effects among women than among men, at least in terms of mortality outcomes (see Doblhammer *et al.*, 2013; van den Berg *et al.*, 2006, 2009, 2011, 2013; Lindeboom *et al.*, 2010; some studies focus mainly or solely on men). However, Yeung *et al.* (2014) report that effects on CVD mortality are stronger among women than among men.

1 In sum, the current paper contributes to the literature by studying the gender-specific
2 effects of the state of the business cycle at birth on cardiovascular disease (CVD) risk in
3 adulthood in post-World War II birth cohorts. Since CVD is the leading cause of death in Europe
4 and around the world (Nichols *et al.*, 2014), it is essential to understand the various causes of
5 CVD over the human lifecycle. Moreover, the early-life conditions literature since its inception
6 has shown that early-life conditions are an important determinant of CVD (see Barker, 1995;
7 Kuh and Ben-Shlomo, 2004; van den Berg *et al.*, 2011; van den Berg and Modin, 2013; Yeung *et*
8 *al.*, 2014). Indeed, the fetal programming hypothesis (Barker, 1995) was formulated specifically
9 in terms of CVD. As discussed above, since our focus is on cohorts born after World War II, the
10 ordinarily used mortality outcomes are not suitable for our analysis. Even actual CVD is not very
11 common among individuals from these cohorts, as they are still relatively young. To proceed,
12 we operationalize CVD *risk*, using biomarker data. Biomarkers enable the observation of a
13 quantitative outcome variable at ages when mortality and morbidity cannot yet be observed. The
14 fact that reliable and consistent biomarkers exist for predicting CVD is an additional advantage
15 of using CVD risk as an outcome. Notice, however, that the literature on the developmental
16 origins of late-life health puts CVD in the same range of outcomes as type-2 diabetes, mental
17 health and cognitive impairments (Barker, 1995; Kuh and Ben-Shlomo, 2004; van den Berg and
18 Modin, 2013; Yeung *et al.*, 2014; Lumey *et al.*, 2011), suggesting that CVD biomarkers are also
19 informative on the risks of those health outcomes.

20 The use of biomarker data has an additional advantage. Policy interventions aimed at
21 preventing high-age CVD have to rely on predictors of CVD such as the biomarkers we
22 examine. If a relation with economic conditions early in life exists then the collection of the
23 relevant biomarker data among adults can be targeted to those born under adverse conditions.

24 We use spatial and temporal fluctuations in the unemployment rate as exogenous indicators
25 of economic conditions early in life. One advantage of this measure, as opposed to GDP, is that

1 it is available at the level of a province for our full observation window. Combining a biomarker-
2 based CVD risk index with provincial level unemployment data enables us to analyse the
3 relationship between adverse conditions at birth and CVD risk later in life.

4 The remainder of the paper is set up as follows. Section 2 describes the data and section 3
5 outlines our empirical strategy. Section 4 presents and discusses our results and the final section
6 concludes.

7 **2. Data**

8 For the purpose of our analysis we combine individual health data from Lifelines cohort
9 study with data on regional unemployment at birth from Statistics Netherlands. Figure 1
10 summarizes these data on a timeline. In what follows we describe each data source in turn and
11 explain the construction of our key variables of interest.

12 [FIGURE 1 ABOUT HERE]

14 **2.1 Lifelines**

15 The biomarker data we use are collected as part of the Lifelines study. Lifelines is a large
16 population-based cohort study and biobank carried out in the northern part of the Netherlands
17 that was established as a resource for research on complex interactions between environment,
18 phenotypic and genomic factors in the development of chronic diseases and healthy ageing. The
19 study adopted three recruitment strategies: recruitment of an index population, aged 25 to 49, via
20 general practitioners (GP), subsequent inclusion of their family members, and online self-
21 registration. Patients who were unable to read Dutch or who had limited life expectancy due to
22 severe illness were excluded by the GP and not invited for participation. The participants visited
23 one of the Lifelines research sites for a physical examination. Also, blood and urine samples
24 were collected, and participants completed extensive questionnaires. The baseline data were
25 collected for 167,729 participants, aged from 6 months to 93 years. Controlling for differences in

1 the demographic composition, the Lifelines adult study population is broadly representative for
2 the adult population of the northern Netherlands (see Klijs *et al.*, 2015, and Scholtens *et al.*,
3 2015, for a detailed description of the study).

4 For the purposes of this paper, Lifelines supplies us with a sample of 95,422 individuals
5 born between 1950 and 1992 (Lifelines Baseline sample, release 201303, made available in
6 2014). The Lifelines baseline interviews and biomarker data collection, on which we base our
7 analysis, was performed between 2006 and 2013. For our analysis, we select only individuals
8 born in the Netherlands, which reduces the sample size to 80,820. Further, we exclude any
9 observations that do not contain all of the information necessary to calculate our main outcome
10 variable (the CVD risk SCORE) such as smoking status, age, gender, total cholesterol and blood
11 pressure. Our final sample consists of 76,566 individuals.

12 The Lifelines study does not include a question on the individual's place of birth, but by
13 linking the Lifelines data to birth certificate data from the Municipal Personal Records Database
14 (in Dutch: *Gemeentelijk Basisadministratie*), we are able obtain information on the province of
15 birth of each sample member. The province of birth is important, as it allows us later to identify
16 the provincial unemployment level at birth. Owing to the high quality of both data sources, no
17 observations are lost in the matching process. While Lifelines contains individuals born all over
18 the Netherlands, births from the three northern provinces are naturally overrepresented. Table 1
19 presents the sample sizes per province.

20
21 [TABLE 1 ABOUT HERE]
22

23 For our purpose, the most important feature of the Lifelines cohort study is that it includes
24 biomarkers concerning cardiovascular disease (CVD) risk, which we can use to construct the
25 Systematic COronary Risk Evaluation (SCORE) index. The SCORE index was developed and

1 validated by the European Society of Cardiology to estimate the 10-year risk of a fatal CVD
2 event. The European Society of Cardiology recommends using SCORE system for assessing
3 individuals' CVD risk in clinical practice in European countries (Pieopoli et al., 2016). In
4 contrast to an actual fatal CVD event (e.g., a major heart attack), the advantage of a surrogate
5 endpoint such as the SCORE index is that we are able to consider relatively younger individuals
6 who are more representative of current cohorts.

7 The SCORE index is constructed according to an algorithm (see Appendix A of Conroy *et*
8 *al.*, 2003) that uses age, gender, smoking status, blood cholesterol levels and blood pressure as
9 inputs to estimate the 10-year absolute risk of a fatal CVD event. We can draw all the constituent
10 parts of the SCORE index from the Lifelines data and are, therefore, able to associate the CVD
11 risk to each individual in our sample. A detailed overview of the CVD risk and in its distribution
12 is contained in Table 2 as well as Figure 1. Both the table and the figure highlight that CVD risk
13 exhibits a strong gender specific pattern. Moreover, we note that CVD risk is strongly skewed,
14 with most individuals displaying limited CVD risk – an issue that we address in the analysis of
15 our results.

16
17 [TABLE 2 ABOUT HERE]

18 [FIGURE 2 ABOUT HERE]

19
20 In addition, to tentatively assess *selection* effects we exploit the fact that Lifelines contains
21 some socioeconomic indicators of the family into which the individual was born, albeit the
22 information is limited. In this respect we use the age of the respondent's mother when he/she was
23 born and whether or not she was smoking during the pregnancy. Both indicators have been
24 shown to have a strong relationship with both, infant health and family's socioeconomic status –
25 with family's from lower socioeconomic groups tending to have children earlier and being more

likely to smoke (Cutler and Glaeser, 2005; Cutler and Lleras-Muney, 2006). The summary statistics of these and our other variables of interest are provided in Table 3.

[TABLE 3 ABOUT HERE]

2.2 Unemployment Data

We proxy the early life conditions by using provincial unemployment data from Statistics Netherlands. The unemployment rate provides us with a contextual variable that serves as a proxy of the socioeconomic conditions under which the individual was born without suffering from the endogeneity of individual level socioeconomic indicators. Provincial level unemployment data are available from 1950 onward, which creates the lower bound for the birth year in the data. We display the development of unemployment between 1950 and 1992 in Figure 2.

[FIGURE 3 ABOUT HERE]

During our sample period, the Netherlands went through all phases of the business cycle multiple times. After World War II, the Netherlands enjoyed a period of substantial economic growth with low associated unemployment rates. At the end of the 1970s and for much of the early 1980s, the Netherlands were hit by a strong recession due to the second oil crisis. This recession was particularly strong in the northern Netherlands where unemployment peaked at well over 10% at the height of the recession. In the early 1990s alongside the world-wide economic boom, unemployment rates dropped significantly all over the country. While the data display a clear common trend among the provinces, we also observe substantial differences in

both levels and trends of unemployment between the provinces. Implying that province-level unemployment data provides us with additional variation from which to identify our relationship of interest.

3. Methods

Our main interest lies in the relationship between unemployment in the birth year and CVD risk later in life. To this end, we start with a simple linear specification with CVD risk as the outcome variable and the provincial unemployment level in the birth year as main explanatory variable. To account for the structure of the data, we also include a birth year and a province fixed effect. We allow the effect of unemployment at birth to be gender specific to account for potential gender differences in the relationship between early-life conditions and health later in life.

Beyond a direct impact on the SCORE index, age can act as a risk factor or as modifier of the other risk factors – the levels of cholesterol and blood pressure increase with age and increase earlier in life in men than in women. Since we already account for birth year fixed effects in the model, there is a risk of multicollinearity if we include also age in the model. However, since the Lifelines data were gathered over a 7-year period (2006-2013), sample members with identical ages can have a variety of different birth years.

Since it is well known in the econometrics that the effects of age on health are highly non-linear, it is important to allow for this non-linearity in the model. Commonly it is done by including a polynomial of age or dummy variables for age categories. However, the coefficients of a polynomial are difficult to interpret while categorizing age omits a lot of available information. An approach that does not have these problems is using a series of linear splines, joined at “knot points”, to model the effects of age (also referred to as “piecewise linear regression”). We control for age in the model by including linear splines with knots at 30, 40, 50

and 60 years. This means that we allow different linear slopes for age from 20 to 30 years, 30 to 40, 40 to 50, 50 to 60 and beyond 60 years of age. Accordingly, the coefficients of the splines can be interpreted as slope coefficients for the respective age groups.

To sum up, we estimate the following specification:

$$CVD_{ipt} = \alpha + \beta_1 u_{pt} * m_i + \beta_2 u_{pt} * f_i + \beta_3 m_i + \sum_{k=1}^K \beta_4 s_{ipt} + \theta_t + \rho_p + \varepsilon_{ipt} \quad (1)$$

where CVD_{ipt} denotes ten-year fatal CVD event risk for individual i born in province p in year t ; u_{pt} is the unemployment rate in province p and birth year t , m_i is a dummy variable taking value 1 if male and 0 if female, while f_i takes the opposite value; s_{ipt} stands for a linear spline with K knots in age of the individual i born in province p and year t ; ρ_p is a province fixed effect, and θ_t is a year-of-birth fixed effect. We estimate the specification in (1) by ordinary least squares (OLS).

Since we are interested in the gender specific effects of unemployment at birth, we have included two interaction terms in the specification – one that interacts unemployment level with a dummy that takes value 1 if the individual is male and 0 if female and one that in interacts unemployment level with a dummy that takes value 1 if the individual is female and 0 if male. Accordingly, to avoid multicollinearity, we do not include the “main” effect of unemployment in the model. This approach allows us to interpret our main parameters of interest, β_1 and β_2 , directly. β_1 represents the marginal effect of unemployment at birth in males while β_2 represents the effect in females.

Since our main explanatory variable – the unemployment level – is measured at the province level, the error terms are likely to be correlated within provinces. Therefore, cluster-robust standard errors are required for statistical inference. The province fixed effects partially control for the within-province correlation, but perhaps not completely. In addition, since there are only 12 provinces in the Netherlands, the number of clusters is small (due to the small sample sizes, the three provinces with smallest number of observations – Limburg, Flevoland

and Zeeland – were grouped together so effectively we have 10 clusters) which means that the estimated variance matrix of the OLS estimator is likely to be downwards biased (Cameron and Miller, 2015). Therefore, we apply the bias-correction of Bell and McCaffrey (2002), which was named CR2VE by Cameron and Miller (2015, p.342 and p. 346), to the standard cluster-robust variance estimates. CR2VE correction implies scaling the province specific vector of residuals \hat{u}_p so that $\tilde{u}_p = (I_{N_p} - H_{pp})^{-0.5} \hat{u}_p$, where $H_{pp} = X_p(X'X)^{-1}X'_p$ with X_p being an $N_p \times K$ matrix, where K is the number of variables included in the model, and N_p is the size of the sample in province p . Stacking X_p over P provinces yields X . In addition, since the number of observations varies considerably across provinces, the effective number of clusters is reduced even further (Imbens and Kolesar, 2016). To address the unbalanced cluster sizes, we base the Wald tests on a $t(v^*)$ -distribution where the degrees of freedom v^* are determined by the data as proposed by Imbens and Kolesar (2016). According to a Monte Carlo study performed by Cameron and Miller (2015), the null hypothesis is rejected too often if we use the “standard formula” for cluster robust standard errors when the number of clusters is small. However, the use of CR2VE residual and of the data-determined degrees of freedom leads to a considerable improvement in inference. That is, the actual size of the t-test (the probability of Type I error given the sample size) is close to the nominal size of the test (the desired significance level α).

4. Results

We present our main estimation results in Table 4, which contains the OLS estimate of the model specified in Equation (1) with the cluster robust standard errors determined as outlined above. The results suggest that while the impact of unemployment at birth on women’s CVD risk is significant at the 1% level – even after taking into account the CR2VE standard errors – the impact of unemployment on men does not differ significantly from zero. Additionally, the test results at the bottom of Table 4 indicate that the coefficient of unemployment in women is

1 statistically significantly different from that in men. More precisely, for women a 1 percentage
2 point increase in the provincial unemployment level leads to a 0.02 percentage point increase in
3 the risk of experiencing a fatal CVD event in the coming 10 years. While this effect may seem
4 relatively small, comparing it to the effect of ageing indicates that, for instance, for a 45 year old
5 woman born when the unemployment rate was elevated by 1 percentage point, the CVD risk is
6 equivalent to that of an identical woman who is 6 months older but born when the
7 unemployment rate was not elevated. Remarkably, regardless of the early-life conditions, men do
8 have a higher CVD risk than women, as is reflected by the substantial point estimate of the
9 gender dummy.

10 Even though Lifelines does not include information about the individual socioeconomic
11 conditions into which a child was born, we do have knowledge of the age of the respondent's
12 mother when he/she was born and whether or not she was smoking. Both indicators have been
13 shown to have a strong relationship with a family's socioeconomic status (SES) – with family's
14 from lower socioeconomic groups tending to have children earlier and being more likely to
15 smoke. Therefore, to partially control for SES, we have added the two indicators to our main
16 specification. The results indicate that while age of the mother is not associated with elevated
17 CVD risk, being born to a mother who smoked is strongly associated to heightened CVD risk
18 later in life.

19
20 [TABLE 4 ABOUT HERE]
21

22 We have performed a range of sensitivity analyses to verify whether the results are robust
23 with respect to aspects of the model specification (results available upon request). First, the
24 impact of early-life conditions on later life outcomes does not seem to be driven by selection
25 effects. Hypothetically, if different women give birth when unemployment is high compared to

1 when unemployment is low, we might observe different health outcomes in the children, even if
2 the causal effect of early life conditions is not present (see, e.g., van den Berg et al., 2018, for a
3 discussion of the literature on cohort composition and business cycles). Thus, if parental SES
4 explains the relationship between unemployment level at birth and CVD risk, we should observe
5 a change in the coefficients of unemployment when we exclude the available parental
6 characteristics (age and smoking status of the mother) from the model. However, the magnitude
7 of the impact of unemployment at birth on CVD risk later in life is essentially unaffected by the
8 two SES variables. This result leads us to believe that selection effects do not rationalize our
9 results. This is also in line with other literature on long-term health effects of conditions at birth
10 that finds that the composition of new-borns does not vary systematically over the business cycle
11 (see *e.g.* Kåreholt, 2001; van den Berg *et al.* 2009 and 2011, and an overview in Van den Berg
12 and Modin, 2013).

13 Second, the key results are not qualitatively affected by other modifications of the
14 specification; that is, sign and significance of the coefficients remain preserved. For example, the
15 results are robust to adding other biomarkers from blood samples to the SCORE index (such as
16 glucose levels and inflammation markers). Results by subintervals of the birth-year window
17 suggest that the effects for females are somewhat stronger for more recent birth cohorts within
18 our observation window. This points to the importance of female labor force participation which
19 started to increase at the national level in the Netherlands only after 1970. Whether this is
20 connected to increased stress exposure is a topic for further research.

21 One exception to the general robustness is found when birth-year fixed effects in the model
22 specification are replaced by a second-degree polynomial in the year of birth. Apparently, the
23 polynomial is not able to capture the effects of the major restructuring of the economy in the
24 early 1980s, or the combination of a low-degree polynomial and an age spline is not sufficiently
25 flexible to fit secular time and age patterns in the data. Also, low-degree polynomials may be

1 less suitable than birth-year fixed effects if the operationalization of the definition of
2 unemployment changes over calendar time or if there are institutional changes in the ease with
3 which transitions into out-of-the-labor-force states such as disability and early retirement can be
4 made. As a final sensitivity analysis, we estimated models for actual CVD occurrence. As
5 expected, due to the low occurrence of CVD, none of the estimated effects is significantly
6 different from zero. The signs of the effects are in line with our results.

7 Finally, since we are working with retrospective data we must discuss two potential
8 sources of bias. First, we are concerned with survivorship bias because we only observe the
9 individuals who have survived till the moment of data collection and are in good enough health
10 to participate. Our results show that women exposed to adverse conditions at birth are at an
11 increased risk for fatal CVD events in adult life. Accordingly, if those men or women who are
12 the most affected by the adverse conditions at birth, do not survive or are unable to participate in
13 the study, our estimates may be biased towards zero. However, the mortality effects of adverse
14 early life conditions have been shown to present only late in life – after the age of 65 (van den
15 Berg et al., 2011). Since our sample contains only participants younger than 65, survivorship
16 bias seem unlikely. Another potential source of bias is the possibility of selective abortion. As
17 argued in van den Berg et al. (2018), the effects of medical abortions can be seen as selection
18 effects, to which our results seem robust. Moreover, even if present, such effects seem to be
19 negligible (van den Berg et al., 2018). However, the potential effects on spontaneous abortions
20 and miscarriages might mean that the individuals who have been affected the most by adverse
21 circumstances might not even be born. Such effects, if present, could also cause bias towards
22 zero in our estimates. However, in the context of the Netherlands after 1950 and considering the
23 rather small magnitude of the effect that we find, spontaneous abortions due to fluctuations in the
24 business cycle seem implausible. To sum up, survivorship bias and selective abortion are

unlikely issues in this study, but in case they are present, our estimates could be considered as conservative or as the lower bound of the true effect.

5. Conclusions

We find that women exposed to unfavorable business-cycle conditions at birth are at an increased risk for fatal CVD events in adult life, among relatively young cohorts of women born after World War II. We interpret this as evidence that unfavorable conditions in the household at birth cause an elevated CVD risk in adult women. The fact that studies using data from much earlier birth cohorts did not unambiguously find strong evidence for such an effect among women may reflect a gradual increase in the size of this causal effect over the past century. This is supported by the finding that the effect is stronger among females born later in our observation window.

For men, CVD risk, on average, is unaffected by early-life exposure to recessions. As explained in the paper, this does not necessarily entail that causal effects of adverse economic conditions at the individual level are absent. Instead, the business cycle might not be capturing fluctuations in economic conditions well, due to improving social safety nets over the 20th century.

There are several possible explanations for the gradual increase in the causal effect in women, and the gender differences in general. First, this gradual increase in women coincides with the increase in female labor force participation, so it is easy to perceive that these two trends might be related and that the effects of exposure in utero might be intensified by the stress of labor participation later in life. Second, compared to pre-war cohorts, smoking and obesity has increased among women from post-war cohorts. There is a consensus in the medical literature that at younger ages (under 50) smoking and type 2 diabetes increases CVD risk in women significantly more than in men (Maas and Appelman, 2010). These risk factors might also magnify the effects of the early life conditions leading to larger and increasing effects in women

1 under the age of 64. However, whether any of these explanations are true remains a topic for
2 further research.

3 To conclude, relatively recent birth cohorts are potentially more representative of current
4 and future cohorts. And the usage of biomarkers allows us to detect elevated health risks well
5 before health events occur. Taken together, this means that the results point at increased risks of
6 actual CVD in the near future for women born when unemployment was high.

7

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Figure 1: Timeline of data sources.

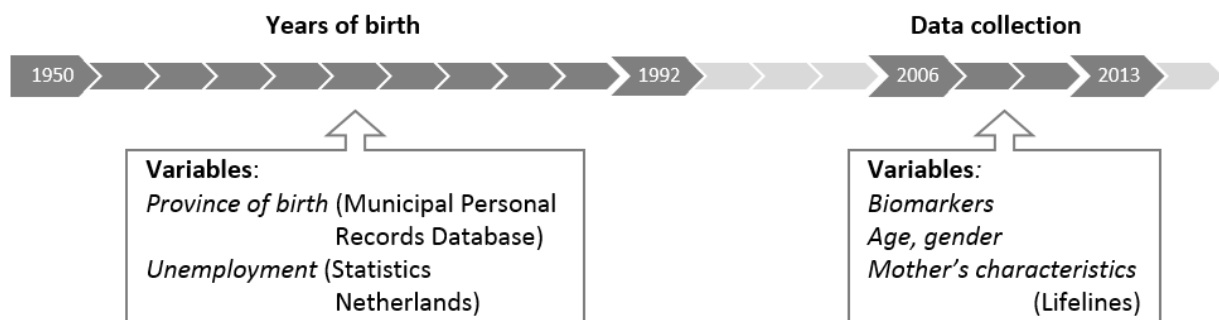


Figure 2: Histograms of absolute 10-year risk of fatal cardiovascular disease event for men and women.

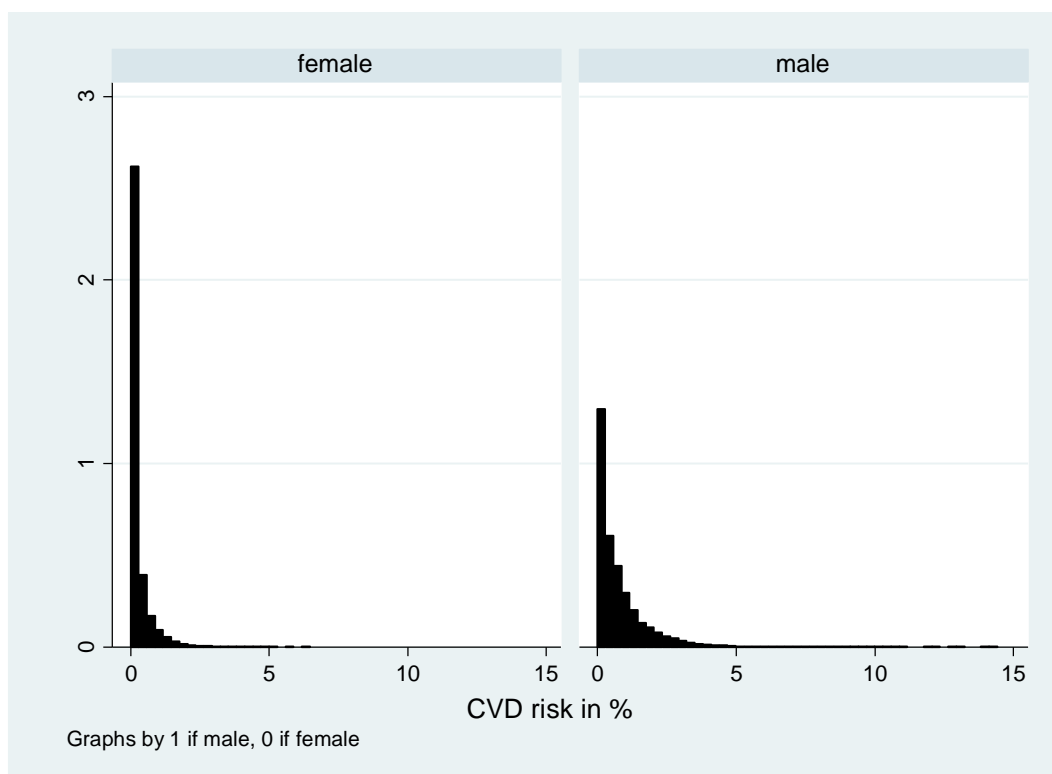
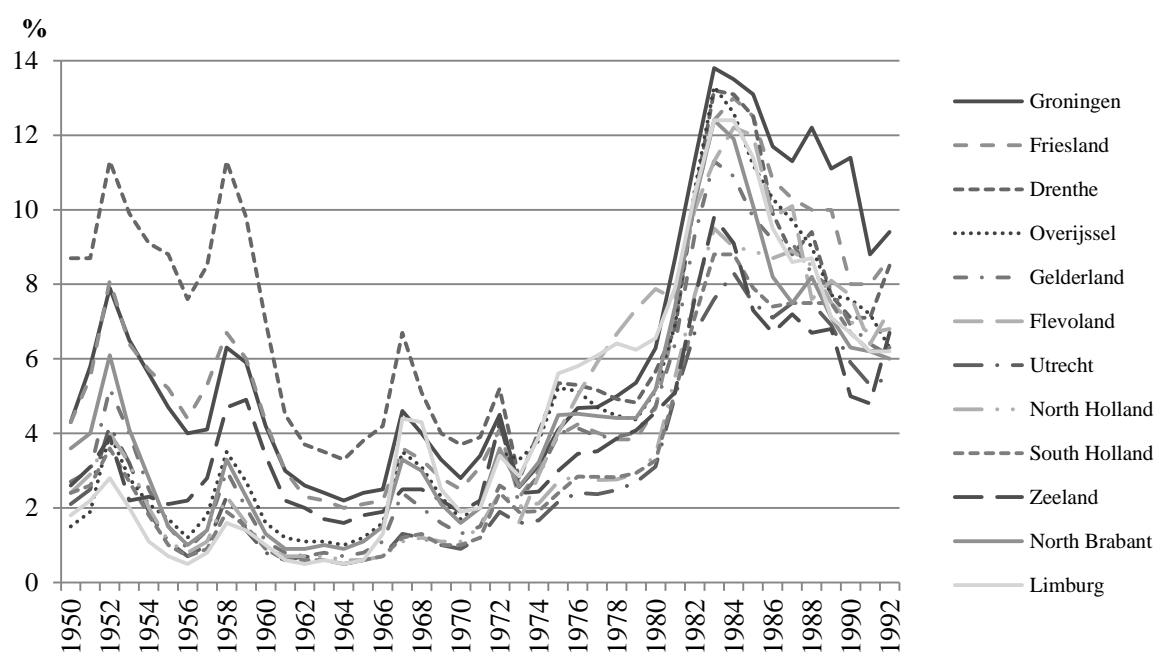


Figure 3: Provincial unemployment level in the Netherlands, 1950-1992



Source: Statistics Netherlands (www.cbs.nl)

Table 1: Sample size per province

Province	Frequency	Percent
Friesland	27,864	36.39
Groningen	22,112	28.88
Drenthe	13,757	17.97
Zuid-Holland	2,955	3.86
Noord-Holland	2,788	3.64
Overijssel	2,684	3.51
Gelderland	1,775	2.32
Utrecht	1,045	1.36
Noord-Brabant	899	1.17
Limburg	350	0.46
Zeeland	182	0.24
Flevoland	155	0.2
Total	76,566	100

Table 2: Detailed descriptive statistics for CVD risk score (%)

	All	Males	Females
<i>Percentiles</i>			
1%	$1.07 \cdot 10^{-4}$	0.003	$7.15 \cdot 10^{-5}$
25%	0.035	0.376	0.015
50%	0.174	0.478	0.085
75%	0.582	1.075	0.268
99%	3.604	4.765	1.908
Observations	76566	31411	45155
Mean	0.470	0.809	0.235
Std. Dev.	0.778	1.025	0.399
Skewness	3.995	3.073	3.758
Kurtosis	30.29	19.13	24.70

Table 3: Descriptive statistics

Variable	Observations	Mean	Std. Dev.	Min	Max
Provincial unemployment rate (%)	76566	4.620	3.031	0.500	13.80
Male	76566	0.410	0.492	0	1
Age at the first visit	76566	42.42	9.526	20.00	63.04
Birth year	76566	1968	9.562	1950	1992
CVD risk score (%)	76566	0.470	0.778	0	14.12

Table 4: CVD risk and unemployment level at birth by gender.

	SCORE CVD death risk %
Female x unemployment	0.021*** <i>0.002</i>
Male x unemployment	-0.006 <i>0.013</i>
Male	0.681*** <i>0.057</i>
Age of mother at birth	-3.5*10 ⁻⁴ <i>0.001</i>
Mother smoked during pregnancy	0.034*** <i>0.006</i>
<i>Linear spline in age</i>	<i>YES</i>
<i>Province fixed effects</i>	<i>YES</i>
<i>Birth year fixed effects</i>	<i>YES</i>
<i>Observations</i>	<i>76,566</i>
<i>IK degrees of freedom:</i>	
female x unemp	6.8
male x unemp	6.9
<i>Test male x unemp – female x unemp</i>	***

Note: OLS regression results. CR2VE standard errors clustered at the province level are reported in italics under the coefficients.

The Imbens-Kolesar degrees of freedom used in the t-tests for the key variables are reported at the bottom of the table. (***) signifies p<0.01, ** signifies p<0.05, and * signifies p<0.1).

Appendix A: Calculating 10-year risk estimates for fatal cardiovascular disease (SCORE) (Conroy *et al.*, 2003).

Step 1: Calculate the underlying risks for coronary heart disease and for non-coronary cardiovascular disease separately for the person's age now and for their age in ten years time, using the values for α and p shown in Table A1. The underlying survival probability, S_0 , is given by:

$$S_0(age) = \exp\{ - (\exp(\alpha))(age-20)^p \}$$

$$S_0(age+10) = \exp\{ - (\exp(\alpha))(age-10)^p \} \quad (1)$$

Step 2: Using the coefficients in Table A2, calculate the weighted sum, w , of the risk factors cholesterol, smoking and systolic blood pressure. Two weighted sums will have to be calculated, one for coronary heart disease and one for non-coronary cardiovascular disease. Smoking is coded as 1 for current and 0 for non-smoker, so no value for smoking has to be entered if the person is a non-smoker. Cholesterol is measured in mmol/L and SBP is measured in mmHg. The weighting for each risk factor is denoted by β .

$$w = \beta_{chol}(cholesterol-6) + \beta_{SBP}(SBP-120) + \beta_{smoker}(current) \quad (2)$$

Step 3: Combine the underlying risks for coronary heart disease and for non-coronary cardiovascular disease, at the person's age and at their age ten years from now (four calculations) which were calculated in step 1 with the weighted sum of a person's risk factors from step 2 for the two end-points, coronary heart disease and non-coronary cardiovascular disease, to get the probability of survival at each age for each cause.

$$S(age) = \{S_0(age)\}^{\exp(w)}$$

$$S(age+10) = \{S_0(age+10)\}^{\exp(w)} \quad (3)$$

Step 4: For each cause, calculate the 10-year survival probability based on the survival probability for the person's current age and their age in 10 years time:

$$S_{10}(age) = S(age+10) / S(age) \quad (4)$$

Step 5: Calculate the 10 year risk for each end-point as

$$Risk_{10} = 1 - S_{10}(age) \quad (5)$$

Step 6: Combine the risks for coronary heart disease and non-coronary cardiovascular disease by adding them:

$$CVDRisk_{10}(age) = [CHDRisk(age)] + [Non-CHDRisk(age)] \quad (6)$$

Table A1: Coefficients for Eq. (1)

		CHD		NON-CHD CVD	
		α	p	α	p
LOW RISK	Men	-22.1	4.71	-26.7	5.64
	Women	-29.8	6.36	-31.0	6.62
HIGH RISK	Men	-21.0	4.62	-25.7	5.47
	Women	-28.7	6.23	-30.0	6.42

Table A2: Coefficients for Eq. (2)

	CHD	NON-CHD CVD
CURRENT SMOKER	0.71	0.63
CHOLESTEROL (MMOL/L)	0.24	0.02
SYSTOLIC BP (MMHG)	0.018	0.018 0.022